EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Executive Director

Letter of Support for Braintale platforms

On 06 December 2021, the Applicant, BrainTale, requested qualification advice for the BrainTale-Research platform as a valid tool to identify and quantify CNS white matter alterations. This approach is based on the use of two platforms: 1) the CE-marked (MDR) medical device BrainTale-Care platform, which is a web-based platform used in several EU hospitals for decision-making in the clinic, and 2) the BrainTale-Research platform used for scientific and/or clinical research.

During its meeting held on 24-27 October 2022, the SAWP agreed on the advice to be given to the Applicant. During its meeting held in December 2022, the CHMP endorsed the advice to be given to the Applicant.

This letter of support is issued based on the review of the qualification advice.

The BrainTale-Research platform is based on calibrated and standardised non-invasive Diffusion Tensor magnetic resonance Imaging (DTI) measurements of cerebral white matter whose performance in reproducibility and repeatability reached minimal requirements recommended by the European Society of Radiology for imaging biomarkers and thus provided sensitive and reliable assessments of central nervous system (CNS) white matter alterations which are systematically linked to clinical status or clinical outcome. Development of BrainTale platform emerged from data acquired in disorders which share as a common feature, a single, temporary noxious stimulus (e.g. head trauma, hypoxia) causing a brain insult. This type of disorders, although presenting with different signs and symptoms depending on the more locally affected regions, has a fairly well-known pathology, and are "static" disorders. The Applicant intends to extrapolate the reasoning from "static" to "progressive" disorders, of different nature (e.g. adrenoleukodystrophy). This initial qualification advice is part of BrainTale's wider objective to establish through the BrainTale-Research platform biomarkers to provide appropriate information about the diagnosis, prognosis and follow-up of patients with neurological or neurodegenerative conditions affecting the white matter and to evaluate therapies developed for these conditions. As such, these biomarkers are expected to serve several purposes in conditions associated with white matter damage (i.e., as diagnostic marker, disease staging marker, prognostic biomarker, biomarker of response to treatment or as surrogate biomarker for clinical outcome ultimately). All these different contexts of use will require a specific validation plan fitted to the intended application setting and within the specific CNS condition of interest.

With this first interaction, the Applicant sought qualification advice on the use of DTI derived indices as biomarker to assess the evolution of the disease and the efficacy of medicines used to treat patients

affected by adrenoleukodystrophy (ALD), amyotrophic lateral sclerosis (ALS), Multiple Sclerosis (MS) and other CNS autoimmune disease. Whereas in ALD there is some relation between the changes in MRI variables indicative of white matter damage and change in clinical outcome in ALD, the data are not robust. Additional evidence would be needed to substantiate this relationship further in ALD. Howewer, this study can be regarded as a proof of concept for this dysmyelinating disorder, but does not allow extrapolations to other demyelinating disorders involving the white matter such as multiple sclerosis or ALS.

Diffusion-tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique, which is used to non-invasively investigate the structure of CNS white matter by enabling visibility of white matter microstructure alterations. DTI-derived parameters are well-known and extensively validated in literature to assess *in-vivo* white-matter microstructure. White matter alterations are involved in pathophysiology of most neurological diseases, either as root cause or as early consequence of pathological events cascade leading to degeneration. For this reason, this technology has been used for years in research to study these diseases. The BrainTale-Research platform which properly quantifies DTI-MRI variables and its dynamics to evaluate white matter alterations from any standard MR devices, could serve several purposes in conditions associated with white matter damages, i.e., as a diagnostic marker, disease staging marker, prognostic biomarker, biomarker of response to treatment or surrogate biomarker for clinical outcome. However, whereas the EMA agreed that there is a large potential with the BrainTale-Research platform, it would be necessary to identify which specific biomarker would be the subject of the qualification, for which specific indication and which specific context of use.

Given the multiple ways by which white matter can be affected within the different families of diseases, it might be appropriate to consider selecting disorders which may cause a strong and early impact in myelin, especially those where changes in myelination status are closely related to symptomatology and disease milestones. To this extent, demyelinating disorders such as leukodystrophies and demyelinating disorders with inflammation (immune, infectious, traumatic) are possibly best suited.

With an initial focus on adrenomyeloneuropathy (AMN) and amyotrophic lateral sclerosis, an incremental approach will have to be taken for the acceptance of the BrainTale-Research platform in other neurological and neurodegenerative conditions. As a reminder, AMN, a form of X-linked adrenoleukodystrophy, is an inherited dysmyelinating condition.

In conclusion, for the time being, BrainTale has not generated enough evidence in relation to any particular context of use, which precludes a qualification opinion at this stage. However, the intention to develop more sensitive markers of CNS white matter alterations and dynamics is encouraged since it could obviously benefit patients. As a result, the EMA supports the general objective of the Applicant to pursue in a staggered approach the qualification of the BrainTale-Research platform expected to be used for scientific and clinical research.

The letter of support is issued on the basis of this qualification advice.

Yours sincerely,

Emer Cooke

Executive Director